PATENT
Docket No. 420522000100

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Brenda Campbell

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In the application of:

Tracy D. WILKINS, *et al.*

Serial No.: 09/545,772

Filing Date: 10 April 2000

For: RECOMBINANT TOXIN A PROTEIN CARRIER FOR POLYSACCHARIDE CONJUGATE VACCINES

Examiner: V. Ford

Group Art Unit: 1645

BRIEF ON APPEAL

MS Appeal Brief – Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

A Notice of Appeal is filed herewith. This is an Appeal from the final rejection, mailed May 5, 2004, of claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39, and 62 in the above-referenced application. In accordance with 37 C.F.R. § 1.192, this Brief, along with the Appendix, is filed **in triplicate** and is accompanied by the required fee.

1. Real Parties in Interest

The real parties in interest in this appeal are the National Institutes of Health by virtue of an assignment recorded in the U.S. Patent and Trademark Office on December 20, 2002,

Reel/Frame: 013312/0882, and TechLab, Inc. by virtue of an assignment recorded in the U.S. Patent and Trademark Office on June 25, 2002, Reel/Frame: 013054/0362.

2. Related Appeals and Interferences

There are no other Appeals or Interferences known to the appellants, the appellants' legal representative, or assignee which will directly affect or be directly affected by or have a bearing on the Board's decision in the present pending appeal.

3. Status of Claims

Claims 1-61 were originally filed. Original claims 2, 4-5, 7-8, 9-12, 16-18, 21-22, 27, 32, 34-35, and 40-60 were canceled in the Amendment under 37 C.F.R. § 1.111, filed August 20, 2001 (claims 40-60), in the Amendment under 37 C.F.R. § 1.111, filed April 26, 2002 (claims 9-12, 16-18, 21-22, 27, 32, and 34-35) and in the Amendment under 37 C.F.R. § 1.116, filed October 15, 2002, (claims 2, 4-5 and 7-8) without prejudice to appellants' right to pursue the subject matter of these claims in subsequent applications. Claims 62-66 were added in the Amendment under 37 C.F.R. § 1.111, filed April 26, 2002. Claims 64-66, directed to methods of using the immunogenic composition of claims 1, 36 or 37, were withdrawn as directed to a non-elected invention according to the Advisory Action, mailed November 26, 2002. Claim 63 was canceled without prejudice in the Amendment under 37 C.F.R. §1.111, filed December 8, 2003. Pending claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39, and 62 have been finally rejected in the Office action mailed May 5, 2004 (page 1 of this Office action erroneously omits claim 33 from its lists of pending and rejected claims). The claims involved in this appeal, claims 1, 3, 6, 13-15, 19-20, 23-26, 28-31, 33, 36-39, and 62, as well as withdrawn claims 64-66, which should be rejoined, are presented in the appendix attached hereto as Exhibit A.

4. Status of Amendments

The Amendment filed by the appellants under 37 C.F.R. §1.111 on December 8, 2003, including amendments to claim 1 and deleting claim 63, has been entered.

5. Summary of the Inventions

The invention is directed to immunogenic compositions where the immunogen of interest is specifically a polysaccharide and where the polysaccharide is administered with a particularly effective carrier, namely, the repeating unit of the *C. difficile* toxin A (*r*ARU). Please see the present specification on page 8, line 28, and page 9, lines 6-7. Appellants have demonstrated the effectiveness of this carrier in the present application, in Example 4 with respect to *Shigella flexneri, E. coli,* and *Pneumococcus*. The vaccines are administered by injection, and the claimed composition is formulated as such, as set forth in Example 4. See page 21, lines 6-10. This formulation is in contrast to U.S. Pat. No. 5,919,463 issued to Thomas *et al.* (Thomas) discussed below which describes the adjuvant effects of toxin A or GST-ARU in an administration route which addresses the mucosa directly. Please see Thomas, *e.g.,* Examples I, II, IVB, and V.

One of the problems encountered in immunizing subjects for protection against infection where the antigen is a polysaccharide is that such polysaccharides may not be sufficiently immunogenic alone to elicit an immune response. Therefore, they require the use of an immunogenic carrier to aid in eliciting an immune response. Such carriers as pertussis toxin, diphtheria toxin, and tetanus toxin have been frequently used; however, overuse of these carriers results in the inability of the subject to later respond to administration of a vaccine for protection against these microorganisms. Please see page 4, lines 8-21 of the present specification. Thus, for example, if tetanus toxoid is used as a carrier, there is a possibility that the subject will no

longer respond to immunization against tetanus. Therefore, it is desirable to provide a variety of carriers in order to prevent overuse of a single type, as provided by the present invention.

6. Issues

a) Whether the finality of the last Office action should be withdrawn.

b) Whether *prima facia* obviousness under 35 U.S.C. § 103 has been established for

1) claims 1, 3, 6, 13-15, 19-20, 23-24, and 36-39 based on Thomas in view of Schneerson *et al.* (Schneerson);

2) claims 1, 3, 6, 13-15, 19-20, 25-26, and 36-39, based on Thomas in view of Taylor *et al.* (Taylor);

3) claims 1, 3, 6, 13-15, 19-20, 28-29, 36-39 and 62 based on Thomas in view of Devi *et al.* (Devi); and

4) claims 1, 3, 6, 13-15, 19, 30-31, 33, and 36-39 based on Thomas in view of Fattom, *et al.* (Fattom);

absent a motivation to substitute Thomas' protein antigens for mucosal administration with each of Schneerson's, Taylor's, Devi's, or Fattom's polysaccharides formulated for injection, wherein *r*ARU is not disclosed as a carrier for a polysaccharide antigen in a formulation for injection.

7. Grouping of Claims

The claims for each ground of rejection stand and fall together.

8. Argument

a) Finality of Office Action Should Be Withdrawn.

The Examiner indicated on page 2 of the May 5, 2004 final Office action that the rejections under 35 U.S.C. §103 (which were nearly identical to those that were withdrawn in the Office action dated July 7, 2003) were necessitated ostensibly because the Applicants amended the phrase "a recombinant protein *and* a polysaccharide component" to "a recombinant protein *conjugated to* a polysaccharide component," and amended "polysaccharide component is *characteristic* of a pathogenic microorganism" to "polysaccharide component is *an antigen* of a pathogenic microorganism." With regard to the first amendment to claim 1, the subject matter of claim 63 was added to claim 1, and claim 63 was canceled. Thus, it is clear that "conjugated to" was not the amendment that necessitated the new ground of rejection, thus providing grounds for the final action. With regard to the amendment to include "an antigen," appellants respectfully submit that "an antigen" does not add subject matter but rather clarifies the phrase "polysaccharide component is characteristic of a pathogenic microorganism." As the rejections are nearly identical to those presented for the first time in the Office action dated November 26, 2002, and withdrawn, it is unclear how this clarifying amendment necessitated the new grounds of rejection. Appellants respectfully submit that this action should not have been made final. Nonetheless, as the issues are nearly identical to the issues presented in the Appeal Brief filed April 10, 2003, which rejections were withdrawn, it is believed that this issue may be moot by virtue of the decision stemming from the obviousness issue below. Otherwise, appellants request the finality be withdrawn.

b) Thomas in Combination with Each of the Secondary References Does Not Render Present Claims Obvious

In the four obviousness rejections outlined in the Issues section above, the Examiner combined Thomas with each of four secondary references that independently discloses the use of particular polysaccharides in a formulation for injection. Therefore, the following arguments are made based on these similarities.

For all of such rejections, the Examiner has not established two elements required for *prima facie* obviousness. First, no motivation is provided to modify and combine the references. Second, no reasonable expectation is provided that a combination would be successful.

i. No motivation to modify or combine references

It is well settled that there must be more than mere disclosure of a species in a secondary reference to arrive at the claimed invention. Rather there has to be a motivation in the references themselves to select the species to arrive at the claimed invention. Please see *In re Jones*, 958 F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992); and *In re Baird*, 16 F3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994). Thomas does not direct a skilled artisan to select polysaccharides as the antigen, nor does Thomas direct a skilled artisan to select the species of *r*ARU to be used as a carrier with the polysaccharide antigen. Moreover, Thomas does not direct a skilled artisan to select a composition formulated for injection comprising a polysaccharide and *r*ARU. In addition, the secondary references do not overcome these deficiencies. Paragraphs a-d below detail such lack of motivation to select a species and modify and combine the references.

a) Thomas Does Not Disclose Polysaccharide Antigen and Provides No Motivation to Select Non-*C. difficile* Antigen

It is respectfully submitted that it is only by the benefit of looking at the appellants' claims that one could choose a polysaccharide antigen, when the whole of Thomas' disclosure directs one to select protein antigens. Specifically, if one looks to the preferred embodiments to determine which compounds are preferred, one will find that Thomas envisions antigens that are proteins such as urease or ovalbumin, or that contain polypeptides such as GST. Please see, *e.g.*, Thomas, column 3, lines 36-37 and Example IV.

Further, even if for the sake of argument polysaccharides were disclosed in Thomas, Thomas does not disclose the claimed polysaccharides, or any other antigen for that matter, that are not *C. difficile* antigens as claimed. In direct contrast to the claim language, Thomas teaches antigens that may be derived from *C. difficile*. Please see Thomas, column 2, lines 63-64.

b) Thomas Provides No Motivation to Select *r*ARU

On page 3 of the Office action dated May 5, 2004, the Examiner points to column 1 in Thomas for a disclosure "that the *C. difficile* toxins contain the ARU which is the carboxy-terminal fragment of *C. difficile* toxins A or B having adjuvant activity." Thomas discloses a myriad of combinations, such as an antigen with a toxin, an antigen with a fragment, or an antigen with a derivative, such as ARU, as disclosed in column 1. It is respectfully submitted that it is only by the benefit of looking at the appellants' claims that one could select *r*ARU derived from the repeat units of *C. difficile* from Thomas' genus of toxins from any bacterium Clostridium species to be used with a polysaccharide. Similarly as discussed above with respect to polysaccharides, the use of *r*ARU as an adjuvant is not sufficiently limited or well-delineated to encompass the specific combination of a polysaccharide and *r*ARU. In looking further at

Thomas' preferred embodiments, Example I is directed to the adjuvant activity of toxin A, with the protein antigen ovalbumin; Example II is directed to toxin A or toxin B with the protein antigen urease; and Example III is directed to a synthesis method for a GST-ARU fusion protein for use as an antigen with adjuvants such as CT or RIBI in Example IV A (please see Thomas column 12, left side of Table 4). This fusion protein was also used as an adjuvant with ovalbumin in Example IV B. Finally, Example V is directed to toxin A and ovalbumin and LT. However, Thomas does not point to *r*ARU as an adjuvant in this or other examples. In other words, the Examiner must pick, choose, and combine various disclosures within Thomas not directly related to each other, in an attempt to arrive at the claimed invention. Therefore, there is no motivation to select an adjuvant that is an *r*ARU fragment from a genus comprising various toxins, derivatives, or fragments, especially when the preferred embodiments point to adjuvants that are toxins, derivatives, or a GST-ARU fusion protein but not an *r*ARU fragment.

c) Thomas Provides No Motivation to Select Injectable Formulation

Further, in the Office action mailed May 5, 2004, the Examiner also alleges, for example on page 4, that "Thomas Jr. et al. disclose that the compositions of the invention can be administered to a patient using standard methods which include oral, rectal, vaginal, intravenous, subcutaneous, or intramuscular routes (column 3)." Only by the benefit of appellants' claims could one select a composition formulated for injection from Thomas' genus of formulations, when, at best, Thomas leads one to select compositions related to Toxin A of *C. difficile* only formulated for mucosal administration. Even if, for the sake of argument, Thomas disclosed polysaccharides, Thomas only discloses *C. difficile* adjuvants in the context of vaccines designed for mucosal administration. Please see, *e.g.,* Thomas, column 1, lines 34-37, Examples I and II (vaccines are administered intranasally), Example IVA (*C. difficile's* Toxin A's repeating units

are coupled to GST as a fusion protein which is an antigen and not an adjuvant as shown in Table 4, left column, but rather used in combination with an adjuvant as shown in Table 4, middle column), Example IVB (vaccine is administered intranasally) and Example V (vaccine is administered to vaginal and rectal mucosal surfaces). Again, the Examiner must pick, choose, and combine various disclosures within Thomas not directly related to each other, in an attempt to be directed to the claimed invention. Thus, hindsight improperly is used, as Thomas discloses the use of a *C. difficile* toxin or derivative as an adjuvant (and not as part of an antigen) in each and every instance as part of a mucosal formulation.

d) Secondary References Provide No Motivation to Select and Combine Components

None of the cited secondary references overcomes the deficiencies discussed above. Each of the secondary references discloses a polysaccharide derived from a particular organism used as a basis for rejection of particular claims. Each of the secondary references describes a polysaccharide conjugated to a protein other than *r*ARU. For example, Schneerson discloses a conjugate vaccine composed of serotype 14 *S. pneumoniae* capsular polysaccharide bound to pertussis toxin, and present claims 23-24 require that the pathogenic microorganism is *S. pneumoniae*. Taylor describes polysaccharide conjugates of *Shigella* polysaccharides with bacterial toxoids, and present claims 25-26 are directed to *Shigella*. Devi describes conjugates of capsular polysaccharides from *N. meningitides* and *E. coli* with tetanus toxoid, and present claims 28 and 29 are directed *to N. meningitides* and *E. coli* respectively. Finally, Fattom describes a conjugate of capsular polysaccharides from *S. aureus* and a *P. aeruginosa* extoxin A, and present claims 31-33 are directed to *S. aureus*.

The Examiner's motivation to combine the references follows the logic in the following simplistic analogy. A primary recipe discloses that protein sources such as chicken and any plant-based product, such as potatoes, work well together, and a secondary recipe discloses that peanut butter and strawberry preserves work well together. Therefore, since chicken and peanut butter are both protein sources and strawberry preserves are plant-based, then certainly, chicken may be substituted for the peanut butter and thus it would obvious and expected, barring any evidence to the contrary, that chicken and strawberry preserves will work well together. As an ordinary food preparer would not be motivated to combine chicken and strawberry preserves, based on the two recipes, likewise, it is respectfully submitted that a skilled artisan would not find it obvious to conjugate *r*ARU (a recombinant protein comprising the toxin A repeating units of *C. difficile*) and a polysaccharide antigen of a pathogenic microorganism which is not *C. difficle*.

As such, there is no motivation to combine the references. Specifically, none of the secondary references mentions *r*ARU, and thus no motivation is provided to use *r*ARU with each of the polysaccharides disclosed in the secondary references, much less use *r*ARU with a composition formulated for injection as claimed. Similarly, none of the secondary references mention that the disclosed polysaccharide can be substituted for Thomas' protein antigens.

ii. No reasonable expectation of success

The Examiner merely suggests that it would be obvious to try the claimed combination and even appears to suggest that such an expectation may be assumed, as discussed further below.

a) "Obvious to Try" is Not Proper Obviousness Standard

The Examiner appears to improperly generalize some disclosure in each of the secondary references, perhaps in an attempt to establish an expectation of success. Even if the references made such generalizations, they would merely suggest that it would be obvious to try other proteins. For instance, on page 5 of the May 5, 2004 Office action, the Examiner alleges that Schneerson demonstrates that "conjugating these capsular polysaccharides to proteins enhances their immunogenicity (3528)." However, there is no such disclosure in this reference that suggests conjugating such a polysaccharide to "proteins" in general, but rather a single protein, pertussis toxin. The Examiner correctly points out that this reference teaches that "polysaccharide protein conjugates for prevention of systemic infections caused by *Haemophilus influenzae* type B serves as a precedent for making conjugates of polysaccharides of other capsulated pathogens." Of course this statement does not relate to the serotype 14 *S. pneumoniae* capsular polysaccharide at issue, but even if it did, such statement may suggest that it is merely obvious to try to make conjugates of other polysaccharides.

Further, on page 7 of the action, with respect to the Taylor reference, the Examiner alleges that Taylor teaches "conjugating these capsular polysaccharides to proteins enhances their immunogenicity (the entire article)." However, the Taylor article describes two protein conjugates, *pseudomonas aeruginosa* exoprotein A (*r*EPA) and tetanus toxoid (TT). Although the abstract refers to the polysaccharides in question as "covalently bound to carrier proteins," it appears that this reference intended to summarize the two carrier proteins described in the article, *r*EPA and TT, rather than carrier proteins in general. Even if the authors intended to suggest that any carrier protein would be effective, such suggestion, again, would merely indicate that other proteins may be obvious to try in a conjugate.

Similarly, on page 9 of the action, the Examiner alleges that Devi teaches "conjugating these capsular polysaccharides to tetanus toxins (carrier proteins) enhances their immunogenicity (the Abstract)." However, Devi's abstract does not extrapolate its tetanus toxin/polysaccharide conjugate results to conjugates comprising carrier proteins in general.

Finally, with respect to Fattom, on page 13 of the action, the Examiner alleges that Fattom teaches "conjugating these capsular polysaccharides to proteins enhances their immunogenicity... (2368)." On this page, or elsewhere in the Fattom article, there is no generalization that conjugating polysaccharides to "proteins" other than exotoxin A would have an effect. There is no disclosure that another protein would enhance immunogenicity. Thus, in this and the other secondary references, the generalized disclosure does not provide a reasonable expectation of success, as the Examiner at best has established that it is merely obvious to try other proteins.

b) Burden of Showing Expectation is Misplaced

In the Office action mailed May 5, 2004, the Examiner alleged on pages 5, 7, 10 and 13, "It would be expected barring evidence to the contrary that [a combination] would be effective." By advancing her position as such, the Examiner appears to suggest that the burden is not on her to show that the combinations are expected to be successful in accordance with MPEP §2143, but rather such expectation is assumed unless the appellants show why it would not be. Such suggestion is not a proper substitute for establishing an expectation of success derived from the references themselves.

As the references themselves do not suggest that a conjugate comprising *r*ARU and a non-*C. difficile* polysaccharide antigen as claimed is expected to be successful, this element for establishing *prima facie* obviousness also has not been established.

As such, it is respectfully submitted that *prima facie* obviousness has not been established for any cited combination of references, and thus, reversal of this rejection is respectfully requested.

9. Appendix

An Appendix containing a copy of the claims as currently pending is attached.

The Assistant Commissioner is hereby authorized to charge any additional fees under 37 C.F.R. § 1.17 that may be required by this Brief, or to credit any overpayment, to Deposit Account No. 03-1952.

Respectfully submitted,

Dated: July 30, 2004

By: _____

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APPENDIX

1. An immunogenic composition for eliciting an immune response to a pathogenic organism which composition comprises a recombinant protein conjugated to a polysaccharide component, wherein said protein comprises the toxin A repeating units (*r*ARU) of *Clostridium difficile* and said polysaccharide component is an antigen of a pathogenic microorganism, which pathogenic microorganism is other than *C. difficile*,

wherein said composition is formulated for injection.

3. The immunogenic composition of claim 1, wherein said polysaccharide component is a capsular polysaccharide or a lipopolysaccharide.

6. The immunogenic composition of claim 1, wherein said protein is a fusion protein.

13. The immunogenic composition of claim 1, wherein said immune response comprises a cellular immune response.

14. The immunogenic composition of claim 1, wherein said immune response comprises a humoral immune response.

15. The immunogenic composition of claim 1, wherein said immune response is protective against said pathogenic microorganism.

19. The immunogenic composition of claim 1, wherein said polysaccharide has been isolated from said pathogenic microorganism.

20. The immunogenic composition of claim 1, wherein said pathogenic microorganism is selected from the group consisting of: *Streptococcus pneumoniae*; *Neisseria meningitidis*; *Escherichia coli*; and *Shigella.*

23. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Streptococcus pneumoniae*.

24. The immunogenic composition of claim 23, wherein said immune response is protective against *Streptococcus pneumoniae*.

25. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Shigella*.

26. The immunogenic composition of claim 25, wherein said immune response is protective against *Shigella*.

28. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Neisseria meningitidis*.

29. The immunogenic composition of claim 20, wherein said pathogenic microorganism is *Escherichia coli* K1.

30. The immunogenic composition of claim 1, wherein said pathogenic microorganism is selected from the group consisting of: *Staphylococcus aureus*; coagulase-negative *Staphylococcus*; *Enterococcus* species; *Enterobacter* species; *Candida* species; and *Pseudomonas* species.

31. The immunogenic composition of claim 30, wherein said immune response is protective with respect to *Staphylococcus aureus*; coagulase-negative *Staphylococcus*; *Enterococcus* species; *Enterobacter* species; *Candida* species; or *Pseudomonas* species.

33. The immunogenic composition of claim 30, wherein said pathogenic microorganism is *Staphylococcus aureus* serogroup 5 or serogroup 8.

36. The immunogenic composition of claim 1 which further comprises a pharmaceutically acceptable carrier.

37. A vaccine comprising the immunogenic composition of claim 36.

38. The vaccine of claim 37, wherein said vaccine is formulated for use in humans.

39. The vaccine of claim 37, wherein said vaccine is formulated for use in animals.

62. The immunogenic composition of claim 28, wherein said immune response is protective against *Neisseria meningitidis*.

64. (Withdrawn): A method to elicit an immune response in a subject to a pathogenic organism which method comprises injecting a subject in need of such response with an effective amount of the immunogenic composition of claim 1.

65. (Withdrawn): A method to elicit an immune response in a subject to a pathogenic organism which method comprises injecting a subject in need of such response with an effective amount of the immunogenic composition of claim 36.

66. (Withdrawn): A method to elicit an immune response in a subject to a pathogenic organism which method comprises injecting a subject in need of such response with an effective amount of the vaccine of claim 37.